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Lung Cancer after Treatment for Hodgkin's Disease: Focus on Radiation Effects

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Aspects of radiation-induced lung cancer were evaluated in an international study of Hodgkin's disease. The study population consisted of 227 patients with lung cancer and 455 matched controls. Unique features included dose determinations to the specific location in the lung where each cancer developed and quantitative data on both chemotherapy and tobacco use obtained from medical records. The estimated excess relative risk (ERR) per Gy was 0.15 (95% CI: 0.06–0.39), and there was little evidence of departure from linearity even though lung doses for the majority of Hodgkin's disease patients treated with radiotherapy exceeded 30 Gy. The interaction of radiation and chemotherapy that included alkylating agents was almost exactly additive, and a multiplicative relationship could be rejected ($P = 0.017$). Conversely, the interaction of radiation and smoking was consistent with a multiplicative relationship, but not with an additive relationship ($P < 0.001$). The ERR/Gy for males was about four times that for females, although the difference was not statistically significant. There was little evidence of modification of the ERR/Gy by time since exposure (after a 5-year minimum latent period), age at exposure, or attained age. Because of the very high radiation doses received by Hodgkin's disease patients and the immunodeficiency inherent to this lymphoma and that associated with chemotherapy, generalizing these findings to other populations receiving considerably lower doses of radiation should be done cautiously.

INTRODUCTION

In a recent international study of Hodgkin's disease patients, excess risks of lung cancer were clearly linked to both the radiation dose and the number of cycles of treatment with alkylating agents (*1*). Unique features of this investigation were its large size (222 Hodgkin's disease patients with lung cancer and 444 matched control patients) and radiation dose determinations to the specific location in the lung where each cancer developed. In addition, detailed data on both chemotherapy and tobacco use were available from medical records.

The current paper provides additional characterizations of radiation-induced lung cancer. More attention is given to the dose–response relationship, to interactions with tobacco use and chemotherapy, and to the modifying effects of gender, age at exposure, time since exposure, and attained age. We also provide additional detail on dose estimation methods and evaluate a simpler approach.

METHODS

Study Subjects

Cases and controls were selected from 19,046 1-year survivors of Hodgkin's disease diagnosed between January 1, 1965 and December 31, 1994 and reported to population-based cancer registries in Connecticut, Iowa, Denmark, Finland, the Netherlands, Ontario (Canada), and Sweden. Record linkage techniques identified 222 lung cancers, which were confirmed by pathology reports and clinical information. Two controls were selected by stratified random sampling for each case and matched by registry, gender, calendar year, age at Hodgkin's disease diagnosis, and cancer-free survival (after Hodgkin's disease diagnosis) for at least as long as the case. Travis *et al.* (*1*) provide further details on study methods. The study was exempted from Institutional Review Board Review since it used only existing anonymized data. Analyses in the current paper include 199 cases and 393 controls from the study of Travis *et al.* (*1*) who had adequate information for radiation dosimetry. In addition, 28 lung cancer cases and 62 matched controls from an earlier Netherlands study (*2*) were added, bringing the total study population to 227 cases and 455 controls. Although the original Netherlands study included 30 cases and 82 matched controls, two cases and 25 controls who did not meet criteria established by Travis *et al.* (*1*) were excluded, and five new controls were selected; the number of matched controls per case in the Netherlands study ranged from one to three. Dosimetry for the Nether-

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lands subjects was updated according to the methods described in the Appendix of this paper.

Data Collection

Medical records were abstracted for demographic information, all therapy for Hodgkin's disease, and smoking history during the matched time interval. Data sources included hospitals, medical centers, radiotherapy departments, and offices of private physicians. Information on chemotherapy included the number of cycles, specific cytotoxic drugs, and cumulative doses, which were reported earlier (*1*).

Detailed smoking histories for patients from the original Netherlands study were obtained as described by van Leeuwen *et al.* (*2*). For patients evaluated in the larger international study (*1*), information was abstracted as available from each record and could include type, amount and status (current use or time of quitting). To minimize possible bias arising from the potential availability of more thorough information on smoking habits for cases than controls, only information collected up to 1 year prior to lung cancer diagnosis (or comparable date in controls) was used in defining smoking status. As an extra precaution against bias, an alternative categorization of smoking status was developed based only on data recorded up to 1 year after Hodgkin's disease diagnosis. Because data on smoking were abstracted from a variety of sources at different times and because a patient's tobacco use could change with time, rules were developed for the assignment of each patient to a category (never smoker, current cigarette smoker, former cigarette smoker, cigar and pipe smoker only, or no information). Subjects were classified as former smokers only if there was reasonable evidence that termination of smoking had occurred at least 5 years prior to lung cancer diagnosis (or comparable date for controls). Estimates of smoking amount in packs per day were also developed. For current smokers, duration of smoking was calculated as the number of years from age 20 to 5 years prior to lung cancer diagnosis. For former smokers, duration was calculated as the number of years from age 20 to the stated date of quitting or, when this date was not available, up to 15 years prior to lung cancer diagnosis (the average quitting time for patients with data available for this variable). Estimates of duration are thus primarily a function of patient age and are subject to error because detailed smoking histories that included data on times of starting and stopping were not available. Pack-years were estimated by multiplying the duration of tobacco use by the estimated smoking amounts. Although we did not estimate pack-years for our previous analyses (*1*), we developed this measure of tobacco use for the current work to allow a more in-depth investigation of the relationship of smoking and radiation exposure.

Radiation dose to the specific location where the lung tumor was located (or comparable location in the matched control patients) was estimated as described in the Appendix.

Statistical Analysis

Conditional regression analysis was conducted with the PECAN module of the software package EPICURE (*3*). The simplest model was one in which the odds ratio, which closely approximates the relative risk, is given by the expression

$$\left[1 + \sum_j \lambda_j x_j\right][1 + \alpha\, ncyc + \beta\, dose], \qquad \text{(Model I)}$$

where the x_j are variables indicating smoking habits (described below), *ncyc* is the number of cycles of treatment with alkylating agents, and *dose* is the radiation dose to the specific location of the tumor expressed in grays. The coefficient β is the excess relative risk per gray (ERR/Gy), a measure that has been used extensively in studies of persons exposed to radiation (*4–6*). Except for analyses that address time since exposure, radiation dose received in the 5 years preceding lung cancer diagnosis (or comparable date in controls) was excluded because other studies have shown a minimum 5-year latent period for radiation-induced lung cancer (*1, 7*). Thus subjects with less than 5 years between diagnoses of Hodgkin's disease and lung cancer (or comparable date in controls) did not contribute to the estimation of parameters that quantify radiation effects. However, these subjects were retained in the analyses because they contribute to the estimation of parameters that quantify the effects of chemotherapy and smoking.

In addition to the model that assumes that risk increases linearly with radiation dose (Model I), we also conducted analyses based on other dose–response functions. These included a categorical model (in which the relative risk was estimated for each of several categories of radiation dose), a linear-quadratic function ($\beta_1\, dose + \beta_2\, dose^2$), and a function that included the possibility of decline in risk due to cell killing at very high doses ($\beta_1\, dose \exp[-\beta_3\, dose]$).

Treatment with alkylating agent chemotherapy is of interest in this paper because of its confounding effects and its interaction with radiation. In the earlier study, we found that inclusion of the number of cycles with alkylating agents as a linear variable (Model I) provided an adequate adjustment for their effects (*1*), and this approach is thus used for all analyses in the current paper. For 11 cases and 17 controls with unknown number of cycles, the median number of cycles (6) was substituted. Patients receiving noncyclic chemotherapy (6 cases and 26 controls) were considered to have no treatment with alkylating agents since there was little evidence of excess risk in this group (RR = 1.3; 95% CI: 0.2–6.7). Earlier, we found that lung cancer risk was increased even in the period 1–5 years after treatment with alkylating agents (*1*), and thus all cycles received 1 or more years prior to lung cancer diagnosis were included.

For most analyses, tobacco use was modeled with four variables: x_1 = pack-years for current smokers; x_2 = pack-years for former smokers; x_3 = indicator variable for patients who smoked only cigars or pipes; and x_4 = indicator variable for patients with no information on smoking. Model I with these four variables was found to provide a significantly better fit than a model with a single pack-year variable for both current and former smokers, or a model based on a log-linear function of the pack-year variables.

With Model I, the effects of radiotherapy and chemotherapy are assumed to add, whereas the effects of smoking and treatment are assumed to multiply. To investigate whether these assumptions are appropriate, we fitted several alternative models, which are described in the sections that address interactions of these variables. These included models in which β was estimated separately by categories of alkylating agent treatment or smoking.

To investigate the possible modifying effects of smoking, time since radiation exposure, sex, age at radiation exposure, attained age (age at lung cancer diagnosis or comparable date in controls), and lung cancer histopathology, we fitted separate coefficients for radiation dose and number of cycles for specific categories of these variables. For age at exposure and attained age, the categories were determined by quartiles among subjects with 5 or more years of follow-up. For smoking, two current smoker *pack-year* categories were determined by the use of the median among current smokers with 5 or more years of follow-up. To evaluate the modifying effects of continuous variables *z*, we fitted the following model and tested $\phi = 0$:

$$\left[1 + \sum_j \lambda_j x_j\right][1 + \alpha\, ncyc \exp(\gamma z) + \beta\, dose \exp(\phi z)].$$

In evaluating the effects of time since exposure, we used the dose received in each of five windows defined by time since exposure. The chemotherapy adjustment for this analysis was based on the time since first treatment with alkylating agents.

Two-sided *P* values and 95% CI were based on the likelihood ratio statistic. Deviances associated with various models are often presented. We remind readers that the smaller the deviance, the better the fit of the model to the data.

RESULTS

Table 1 shows the distribution of cases and controls by registry and treatment. After excluding patients with insuf-

TABLE 1
Numbers of Lung Cancer Cases and Matched Controls by Registry and Treatment Category

	Cases	Controls
Total	227	455
A. Subjects from Travis *et al.* (*1*) by registry		
Connecticut	22	43
Denmark	36	70
Finland	21	42
Iowa	17	32
Netherlands	9	18
Ontario	62	124
Sweden	32	64
Total from Travis *et al.* (*1*)[a]	199	393
Netherlands subjects from van Leeuwen *et al.* (*2*)[b]	28	62
B. Treatment category		
Radiotherapy with positive 5-year lagged dose[c]	146	271
Cyclic AA[d]: No	78	165
Cyclic AA: Yes	68	106
Radiotherapy, but all treatments within 5 years of lung cancer diagnosis[e,f]	38	97
Cyclic AA: No	15	58
Cyclic AA: Yes	23	39
No radiotherapy at any time[g]	43	87
Cyclic AA: No[h]	3	17
Cyclic AA: Yes	40	70

[a] Only subjects with adequate radiation dosimetry are included (see Table A1).

[b] Included in Van Leeuwen *et al.* (*2*) but not in Travis *et al.* (*1*).

[c] The 5-year lagged dose is the dose received more than 5 years before the date of lung cancer diagnosis (or comparable date in controls). Only subjects for whom radiation doses could be estimated are included. See Appendix Table 1.

[d] AA = treatment with alkylating agents.

[e] For 2 cases and 7 controls, data were inadequate for dose estimation.

[f] For 35 cases and 84 controls, the time between Hodgkin's disease and lung cancer diagnosis was less than 5 years; for 3 cases and 13 controls, this interval was 5 or more years.

[g] For 19 cases and 24 controls, the time between Hodgkin's disease and lung cancer diagnosis was less than 5 years; for 24 cases and 63 controls, this interval was 5 or more years.

[h] One case and 11 controls were treated with noncyclic AA; 2 cases and 6 controls were treated with cytotoxic drugs that did not include AA.

ficient information for dose estimation (23 cases, 41 controls; see Appendix), 682 patients (227 cases and 455 controls) were included in the analyses. Of these, 552 (184 cases and 368 controls) received radiotherapy, and 417 of the 552 (146 cases and 271 controls) received radiotherapy 5 or more years before lung cancer diagnosis (or comparable date in controls). Most radiotherapy was given shortly after Hodgkin's disease diagnosis, so that 94% of the dose was received within 1 year of diagnosis. In contrast, 35% of the 346 patients given cyclic alkylating agent treatment received at least part of this treatment a year or more after Hodgkin's disease diagnosis, and 21% received all such treatment in this period.

Table 2 shows the results of fitting Model I. In addition to the excess relative risk (ERR) coefficients, the table shows relative risks at the median values for continuous variables. All variables in this model show significant associations with lung cancer risk. The risk of lung cancer per pack-year of cigarette smoking is more than three times as large for current smokers as for former smokers. The relative risk for patients with no information on smoking is lower than that for other smoking categories, suggesting that this category may be comprised mainly of nonsmokers and former smokers.

In fitting Model I, we evaluated each of the seven registries for significant departures of the coefficients for radiation dose and number of alkylating agent cycles from common values. The only instance of such a departure was for the Netherlands *ncyc* coefficient, which was −0.027 per cycle (95% CI: <0–0.23) and was significantly lower than the value obtained from the remaining registries ($P < 0.001$). Because of this finding, the *ncyc* coefficient was set equal to zero for Netherlands patients for the analyses in Table 2 and for all subsequent analyses. The Netherlands estimate for the radiation coefficient of 0.06 per gray (95% CI: −0.002–0.35) was also smaller than that for the remaining registries [0.21 (95% CI: 0.07–0.65)], but the difference was not significant ($P = 0.22$). Because both the effects of chemotherapy and the data collection methods were different for Netherlands patients (*2*) than for patients included in the large international study (*1*), we repeated most analyses in this paper with Netherlands subjects excluded; in no case were results substantially altered.

Dose–Response Analyses

Figure 1 depicts the dose distribution for cases and controls, and Table 3 shows numbers of cases and controls and relative risks by dose category. The dose distribution is bimodal, with most subjects having doses either less than 5 Gy or more than 30 Gy, depending largely on whether or not the tumor (or the comparable location in controls) was in an unblocked region of a chest field. Estimating separate relative risks for each of the five dose categories in Table 3 gave a nearly identical fit to the linear model (Table 2), indicating that the linear model provided a good fit (deviances for the categorical and linear models were 353.66 and 354.53, respectively). Neither adding a dose-squared term nor adding a term to reflect a decline in risk due to cell killing significantly improved the fit ($P > 0.5$ in both cases), again indicating the good fit of the linear model. The linear model fitted the data significantly better than just including an indicator for radiation treatment ($P < 0.001$) or an indicator for dose over 1 Gy ($P = 0.005$), but only marginally better than just including an indicator for dose greater than 5 Gy ($P = 0.081$) or dose greater than 30 Gy ($P = 0.11$). When the ERR/Gy was estimated using

TABLE 2
Excess Relative Risk per Unit of Exposure to Smoking, Alkylating Agents, and Radiotherapy[a]

Variable description	Units	Cases	Controls	Excess relative risk (ERR) per unit (95% CI)	Median	Relative risk at median (95% CI)
Smoking						
Never smokers	Yes/No	7	96	0.0		1.0
Current smokers	Pack-years	157	178	0.72 (0.29–2.09)	32 pack-years	24.0 (10.3–68)
Former smokers	Pack-years	26	73	0.23 (0.073–0.74)	25 pack-years	6.8 (2.8–19.5)
Cigar/pipe only	Yes/No	13	25	12.4 (3.26–46)		13.4 (4.3–47)
No information on smoking	Yes/No	24	83	3.8 (0.86–13.5)		4.8 (1.9–14.5)
Alkylating agents						
No		110	282	0.0		1.0
Yes	Cycles[b]	117	173	0.75 (0.30–1.83)	6 cycles	5.5 (2.8–12.0)
Radiotherapy						
No		43	87	0.0		1.0
Yes, all treatment within 5 years of lung cancer diagnosis[c]		38	97	0.0		1.0
Yes, treatment 5 or more years before lung cancer diagnosis	Dose in Gy[d]	146	271	0.15 (0.057–0.39)	32 Gy	5.8 (2.8–13.5)

[a] Based on Model I as described in the Statistical Methods section.
[b] Number of cycles of treatment with alkylating agents (included for all registries except the Netherlands).
[c] Dose during this period is assumed to be ineffective in increasing lung cancer risk.
[d] Dose received 5 or more years before lung cancer diagnosis.

only doses less than 30 Gy, it did not differ significantly from zero ($P = 0.13$), although the estimate of 0.12 was similar to the estimate of 0.15 based on the full dose range. We also fitted a model in which the ERR/Gy was estimated separately for dose received within 1 year of Hodgkin's disease diagnosis and dose received later; the two coefficients were very similar, 0.15 and 0.17 per gray, respectively. Repeating these analyses with the alternative smoking adjustment (based only on data collected within 1 year of Hodgkin's disease diagnosis) did not greatly modify these results.

Interaction of Radiation and Treatment with Alkylating Agents

The model displayed in Table 2 is based on the assumption of an additive relationship between radiotherapy and treatment with alkylating agents. A multiplicative model of the form

$$\left[1 + \sum_j \lambda_j x_j\right][1 + \alpha\, ncyc][1 + \beta\, dose] \qquad \text{(Model II)}$$

did not fit the data as well as the additive model I (deviances were 360.24 for Model II and 354.53 for Model I). We also fitted the general model,

$$\left[1 + \sum_j \lambda_j x_j\right][1 + \alpha\, ncyc + \beta\, dose + \gamma\, ncyc \times dose],$$

which includes both Model I ($\gamma = 0$) and Model II ($\gamma = \alpha\,\beta$) as special cases. The deviance for this general model was 354.50, nearly identical to that obtained with the additive model, and thus indicated the good fit of the additive Model I. The estimated coefficients were $\alpha = 0.75$, $\beta = 0.15$, $\gamma = 0.001$, and the multiplicative Model II could be rejected ($P = 0.017$).

Table 4 shows analyses in which the parameters α and β in Model I are estimated separately by categories of several variables. The numbers of cases and controls shown in the ''exposed'' column include all patients whose 5-year lagged radiation doses were greater than zero. The numbers in the ''unexposed'' column include patients for whom this dose was zero and who were also followed for at least 5 years. As noted earlier, subjects with less than 5 years of follow-up do not contribute to estimation of radiation parameters. The analyses in Table 4A and B are relevant to the interaction of radiotherapy and treatment with alkylating agents, and indicate that, based on the additive Model I, the effects of radiation (ERR/Gy) were similar for groups defined by whether or not patients were also treated with alkylating agents and by the timing of this treatment.

Interaction of Treatment and Smoking

Investigation of the interaction of treatment and smoking is complex, because neither exposure could be modeled adequately with a single variable. Model I is based on the assumption that the effects of smoking multiply the combined effects of radiotherapy and treatment with alkylating agents. We also fitted the additive model in which the relative risk is

$$1 + \sum_j \lambda_j x_j + \alpha\, ncyc + \beta\, dose. \qquad \text{(Model III)}$$

With this model, convergence could not be achieved unless

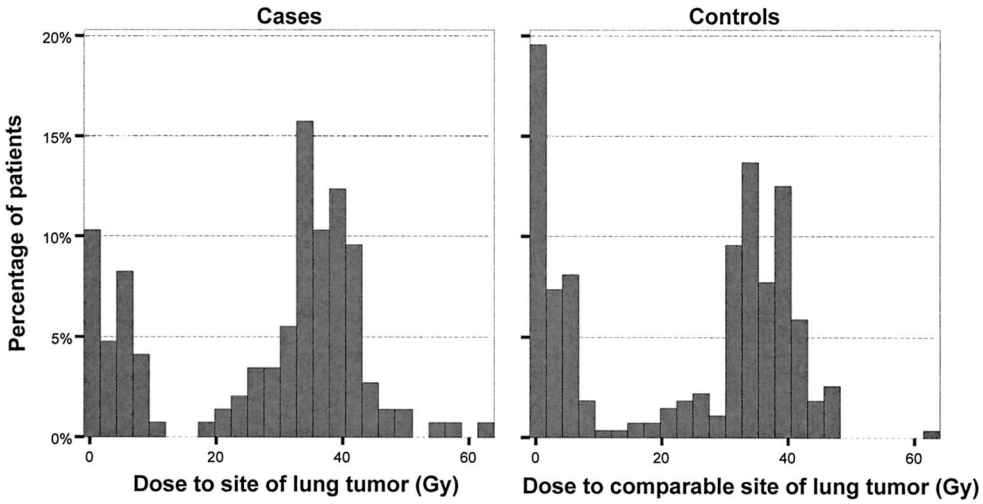

FIG. 1. Absorbed radiation dose (Gy) to lung tumor sites for cases and controls (excluding dose received in the 5 years preceding lung cancer diagnosis or comparable date in controls).

we omitted the indicator for patients with no information on smoking (x_4); with this variable omitted, such patients are included in the referent category along with never smokers. This model did not fit the data nearly as well as Model I without the x_4 variable (the respective deviances were 403.40 and 365.57). There are many possible departures from Models I and III that might be investigated. We evaluated the addition of terms γ *z*ncyc* and ϕ *z*dose* and tested $\phi = 0$, where *z* was taken to be *pack-years* (combining current and former smokers) or one of two linear functions of the smoking variables x_j. The variable *smokemult* was calculated as $\Sigma_j \lambda_j x_j$ using coefficients shown in Table 2 and was used to evaluate departures from the multiplicative model, whereas the variable *smokeadd* was calculated using analogous coefficients from fitting Model III and was used to evaluate departures from the additive model. There was no evidence of departure from Model I ($P = 0.30$ for *pack-years* and $P > 0.5$ for *smokemult*), but strong evidence of departure from Model III ($P = 0.02$ for *pack-years* and $P < .001$ for *smokeadd*). Results of testing $\gamma = 0$ were similar, indicating that a multiplicative relationship of smoking and treatment with alkylating agents was compatible with the data whereas an additive relationship was not.

Also relevant to the radiation–smoking interaction, Table 4C shows separate estimates of the ERR/Gy for five smoking categories. Although the test for homogeneity among the five categories does not provide strong evidence of departure from a multiplicative model, the risks are highest among current smokers with 32 or more pack-years and among cigar and pipe smokers (although the ERR/Gy for the latter group is estimated very uncertainly). The ERR/Gy among never and unknown smokers or among former smokers did not differ significantly from zero ($P = 0.092$ and 0.48, respectively). However, if these categories were combined, the ERR/Gy was 0.055 (95% CI: 0.002–1.29) and differed significantly from zero ($P = 0.033$).

The analyses described in this section were repeated using only smoking data collected within 1 year of Hodgkin's disease diagnosis. Results were generally similar, although

TABLE 3
Numbers of Lung Cancer Cases and Matched Controls and Relative Risks (RR) by Category of Radiation Dose

Dose category	Cases	Controls	Relative risk[a] (95% CI)	Two-sided *P* value for ERR = 0[b]
No radiotherapy	43	87	1.0	
Radiotherapy with time since treatment less than 5 years[c]	38	97	1.0	
Radiotherapy with time since treatment 5+ years				
>0–4.9 Gy	27	84	1.64 (0.53–5.2)	0.39
5.0–14.9 Gy	14	18	4.18 (0.70–21)	0.11
15.0–29.9 Gy	14	22	2.69 (0.15–15)	0.40
30.0–39.9 Gy	60	102	8.50 (3.3–24)	<0.001
40.0+ Gy	31	45	6.27 (2.2–19)	<0.001

[a] Adjusted for number of cycles with alkylating agents and smoking.
[b] Two-sided *P* value for testing the null hypothesis that the ERR (RR − 1) is equal to zero.
[c] Dose during this period is assumed to be ineffective in increasing lung cancer risk.

TABLE 4
Excess Relative Risk (ERR) per Gray by Categories of Chemotherapy, Smoking, Sex, Time since Exposure, Age at Hodgkin's Disease Diagnosis, Attained Age, and Histopathological Type of Lung Cancer[a]

Variable description	Unexposed to radiation[b] cases/controls	Exposed to radiation[c] cases/controls	Excess relative risk (ERR) per Gy[d] (95% CI)	Two-sided *P* value for testing ERR/Gy = 0
A. Number of cycles of treatment with alkylating agents				
0	2/29	86/189	0.15 (0.056–0.39)	<0.001
1–6	15/22	36/58	0.15 (0.001–0.57)	0.048
>6	10/25	24/24	0.17 (−0.09–1.05)	0.26
P value for homogeneity			>0.5	
P value for trend[f]			>0.5 (−)	
B. Time of treatment with alkylating agents (AA)[e]				
No AA treatment	2/29	86/189	0.15 (0.057–0.40)	<0.001
AA within 1 year of Hodgkin's disease diagnosis	24/47	31/54	0.10 (−0.04–0.51)	0.20
AA but not within one year of Hodgkin's disease diagnosis	1/0	29/28	0.24 (0.005–0.98)	0.043
P value for homogeneity			>0.5	
C. Smoking				
Never smokers and unknown	1/33	21/108	0.042 (−0.003–0.29)	0.092
Current smokers <32 pack-years	6/13	49/56	0.095 (0.019–0.33)	0.001
Current smokers 32+ pack-years	13/17	52/42	0.35 (0.095–1.19)	<0.001
Former smokers	6/11	16/52	0.021 (−0.017–0.27)	0.48
Cigar/pipe only	1/2	8/13	0.42 (0.018–11.0)	0.14
P value for homogeneity			0.17	
D. Sex				
Males	22/59	107/200	0.18 (0.063–0.52)	<0.001
Females	5/17	39/71	0.044 (−0.009–0.53)	0.20
P value for homogeneity			0.30	
E. Time since exposure[g]				
1–5 years	18/23	38/93	0.006 (−0.019–0.11)	>0.5
5–10 years	11/28	59/106	0.18 (0.036–0.81)	<0.001
10–15 years	9/20	37/73	0.15 (0.029–0.69)	<0.001
15–20 years	3/6	25/48	0.13 (0.006–1.09)	0.026
20+ years	1/9	23/41	0.070 (<0–0.85)	0.15
P value for homogeneity			>0.5	
P value for trend[f,h]			>0.5 (−)	
F. Age at Hodgkin's disease diagnosis				
<37 years	1/10	42/77	0.33 (0.020–>100)	0.006
37–47.9 years	4/14	40/76	0.051 (−0.007–0.48)	0.14
48–55.9 years	10/20	34/69	0.088 (0.005–0.42)	0.026
56+ years	12/32	30/49	0.36 (0.073–1.93)	<0.001
P value for homogeneity			0.42	
P value for trend[f]			0.44 (+)	
G. Age at lung cancer diagnosis				
<51 years	2/11	39/72	1.15 (0.030–>100)	0.003
51–58.9 years	2/11	42/79	0.062 (0.000–0.32)	0.050
59–66.9 years	12/22	33/68	0.13 (0.011–1.05)	0.013
67+ years	11/32	32/52	0.61 (0.086–6.4)	<0.001
P value for homogeneity			0.30	
P value for trend[f]			0.34 (+)	
H. Histopathological type of lung cancer				
Squamous cell	18/37	60/119	0.13 (0.027–0.57)	<0.001
Small cell	6/13	24/48	0.12 (−0.001–1.60)	0.053
Adenocarcinoma	0/10	30/51	0.47 (0.054–>100)	0.001
Large cell	1/8	12/18	2.00 (0.061–>100)	0.004
Other	2/8	20/35	0.0032 (−0.022–0.41)	>0.5
P value for homogeneity			0.27	

[a] Based on Model I as described in the Statistical Methods section.
[b] Excludes 54 cases and 108 controls with less than 5 years between Hodgkin's disease and lung cancer diagnoses. These patients contribute to the

for the analysis shown in Table 4C, there was less evidence of heterogeneity ($P = 0.38$) and the ERR/Gy for current smokers with 32 or more pack-years was smaller than that for current smokers with less than 32 pack-years. Also, the ERR/Gy among never and unknown smokers was larger, 0.11 (95% CI: 0.014–0.64), and differed significantly from zero ($P = 0.004$).

Interaction of Treatment and Other Variables

Table 4D shows ERR/Gy by sex. Although not significantly different, the ERR for females is smaller than that for males and does not differ significantly from zero ($P = 0.20$). Because both Hodgkin's disease and lung cancer are more common in males than in females, only about a quarter of the subjects were female. The sex-specific ERR/Gy were also calculated with separate *pack-year* variables for the two sexes, which did not greatly modify results.

Table 4E shows estimated ERR/Gy for categories defined by time since exposure. These analyses are based on 11 fewer subjects (3 cases and 8 controls) than other analyses because of the need to have estimable radiation doses even if all radiotherapy was within 5 years of lung cancer diagnosis. There was no evidence of increased risk for radiation dose received within 5 years of lung cancer diagnosis, and a model with separate coefficients for the dose within this period and the 5-year lagged dose (deviance = 347.04) fitted the data significantly better ($P = 0.008$) than a model with a single coefficient for unlagged dose (deviance = 354.11). The fit of the model with two coefficients was nearly identical to a model that included only the 5-year lagged dose (347.07) and was also similar to the model shown in Table 4E with five separate coefficients (346.57).

Table 4F shows results by age at Hodgkin's disease diagnosis. Since 94% of the radiation dose was received in the first year after Hodgkin's disease diagnosis, age at Hodgkin's disease diagnosis is nearly identical to age at exposure. Although the test for trend was not close to statistical significance, this may have been because the ERR decreased and then increased with increasing age at Hodgkin's disease diagnosis. A similar relationship was observed for age at lung cancer diagnosis, and tests do not indicate statistical significance (Table 4G).

Table 4H compares ERR/Gy by the histopathological type of lung cancer. No evidence of heterogeneity is found, although the ERRs are highest for adenocarcinoma and large cell carcinoma.

Dosimetry Issues

Unlike previous analyses addressing lung cancer risk in Hodgkin's disease patients, our analyses were based on doses to the specific site of the lung tumor. Because this approach required extensive efforts to determine tumor location and to obtain detailed information on radiotherapy, we were interested in comparing our results with those based on other dose estimation methods requiring less intensive approaches. Thus the average dose to each lobe of the two lungs was estimated based on typical blocking conditions that did not require either detailed radiotherapy records or precise tumor location for individual patients. The average dose estimate for a particular patient was then taken to be the dose to the lobe where the tumor was located. This approach is similar to that used by van Leeuwen *et al.* (*2*) except that our method took account of information on standard blocking, acquired from review of simulator films of chest fields. Information on tumor location was obtained from medical records, and patients without such data (23 cases, 39 controls) were excluded from these analyses. Among patients with positive 5-year lagged dose, the mean dose to the specific site where the lung cancer was diagnosed was 24.2 Gy, while the mean dose to the lobe was 15.8 Gy.

With Model I, analyses using lobe doses (deviance = 321.18) did not fit the data as well as analyses using doses to the specific tumor site (deviance = 315.03). A significant improvement in fit ($P = 0.006$) was achieved when dose to the specific tumor site was added to a model based on the lobe dose. For dose to the specific tumor location, the estimated ERR/Gy (based on this subset of the data) was 0.12 (95% CI: 0.04–0.35), whereas for the lobe dose, the estimated ERR/Gy was 0.19 (95% CI: 0.05–0.60), a difference that reflects the differences in mean doses for the two methods. A measure of the relative uncertainty can be obtained as the ratio of the length of the CI to the ERR/Gy. The value of 2.58 for the doses to the specific tumor lo-

←

estimation of smoking and chemotherapy parameters, but are uninformative for estimating the ERR/Gy.

[c] Treated with radiation 5 or more years before lung cancer diagnosis.

[d] Adjusted for number of cycles with alkylating agents and smoking.

[e] Netherlands patients were included in the no AA treatment (0 cycles) category.

[f] Trend tests are based on continuous variables. The direction of the trend is indicated in parentheses.

[g] Based on dose in each exposure window. Unlike other analyses in this table, numbers of unexposed cases and controls include patients with less than 5 years between Hodgkin's disease and lung cancer diagnoses. Numbers of exposed cases and controls are based on the period with largest dose, which was usually close to the time of Hodgkin's disease diagnosis. Radiation doses received in the period 1–5 years before lung cancer diagnosis are included, and thus, unlike other analyses in this table, it was necessary to exclude an additional 3 cases and 8 controls (including 2 cases and 7 controls who received radiotherapy in this period, but whose doses could not be estimated; 1 case and 1 control who did not receive radiotherapy, but were in matched sets of subjects with doses that could not be estimated).

[h] Results are based on 5-year lagged dose and include only 5+ year periods.

TABLE 5
Estimates of the ERR/Gy for Lung Cancer from Selected Studies[a]

Study	Number of lung cancers[b]	Mean dose in Gy (range)	Type of exposure
Hodgkin's disease patients (this study)	146	25 (0.02–64)	Partial-body, fractionated
A-bomb survivors (mortality) (*6*)	939[c]	NA[d]	Whole-body, single acute dose
A-bomb survivors (incidence) (*5*)	449	0.23 (0.01–~4)	Whole-body, single acute dose
Ankylosing spondylitis patients (*16*)	563	8.9 (0.8–16.3)	Partial body, fractionated
Canadian fluoroscopy patients (*17*)	455	1.0 (0–24)	Partial body, fractionated
Male Mayak workers (*18*)	191[c]	1.2 (0–>5)	Partial body, fractionated
Peptic ulcer patients (*19*)	125	1.8 (NA[d])	Partial body, fractionated
Female breast cancer patients (*20*)	17	15.2 (0.1–22.6)	Partial body, fractionated
Female benign breast disease patients (*21*)	10	0.75 (0.004–9.0)	Partial body, fractionated

[a] Studies are limited to those that involved low-LET radiation exposure, and in which estimates of the ERR/Gy based on dose-response analyses were presented.
[b] Number of exposed cases unless indicated otherwise.
[c] Includes both exposed and unexposed cases.
[d] Not available.
[e] Estimates are from appendix tables AII, AIII, and AIV (*6*).
[f] Estimates and CI for sex-specific estimates calculated from RERF data set since CI for these estimates were not available in ref. (*5*).
[g] 83% of subjects were males.
[h] Estimate based on first 25 years of follow-up.
[i] Estimate for external low-LET dose, adjusted for plutonium dose.

cation is somewhat smaller than the value of 2.91 for the lobe doses.

We also estimated an average dose for the entire lung, where the dose to each specific lobe of the lung was weighted by the proportion of cases with tumors in that lobe. To the number of decimal places shown, the ERR/Gy and 95% CI based on this approach were identical to the estimate based on the lobe-specific doses, with little evidence of improvement in fit when the lobe-specific dose was added to a model that included the overall average dose ($P > 0.5$).

Estimates of dose to the specific lung tumor site are subject to uncertainties in determining the tumor location, particularly for tumors that are located near the ''edge'' of a block or radiation field. To investigate the possible impact of this uncertainty, we conducted an analysis in which ERR/Gy were estimated separately for patients whose tumors were within 2 cm of an ''edge'' and for the remaining patients whose tumors were not near an edge. Of subjects with positive 5-year lagged doses (146 case and 271 controls), 38 cases and 62 controls had tumors within 2 cm of an edge; the estimated ERR/Gy for this group (0.146) was nearly identical to the estimate of 0.152 for remaining patients.

DISCUSSION

Lung cancer risk has been clearly linked with exposure to ionizing radiation in many human studies (*4*), including our investigation. In previous studies of lung cancer after radiotherapy for Hodgkin's disease (*2, 8, 9*), a dose response was demonstrated only by van Leeuwen *et al.* (*2*). In analyses by Kaldor *et al.* (*8*), a dose response was suggested only for subjects who were treated with radiotherapy alone, while Swerdlow *et al.* (*9*) found no evidence of a radiation dose response. These differences (*8, 9*) might be explained by the relatively small numbers of subjects and imprecise radiation dosimetry that did not consider either tumor location or standard blocking of lung. In addition, quantitative data on tobacco habits were not collected in either study; less than 40% of the subjects in the study by Swerdlow *et al.* (*9*) had information on smoking.

The majority of patients who were treated with radiotherapy in our study received doses to the specific tumor location that exceeded 30 Gy, and the association between radiation dose and risk of lung cancer was largely driven by the risks observed for these subjects. Although a linear dose–response function provided a good fit to the data, the relatively small number of subjects at lower doses may have limited our ability to detect any decline in risk at higher doses due to cell killing, as observed for exquisitely radiosensitive organs, such as bone marrow (*10*). Radiotherapy of the lung is, however, associated with cellular proliferation, atypical pneumocyte hyperplasia, fibrosis, and squamous metaplasia (*11–13*) with the subsequent transformation and expansion of premalignant clones. Genetic alterations, consisting of microsatellite instability or loss of heterozygosity, are evident in sputum samples from 50% of patients with pulmonary fibrosis (*14*), which may be caused by radiotherapy (*13*) and may predispose to lung cancer (reviewed in ref. *15*).

Table 5 summarizes data on lung cancer risks from several studies of low-LET radiation exposure, and includes most investigations in which estimates of the ERR/Gy based on dose–response analyses were presented (*5, 6, 16–21*). A number of factors might contribute to the variation

TABLE 5
Extended

Excess relative risk per Gy (95% CI)		
Males	Females	All subjects
0.18 (0.063–0.52)	0.044 (−0.009–0.53)	0.15 (0.057–0.39)
0.34[e] (0.06–0.69)	0.89[e] (0.41–1.51)	0.53[e] (0.28–0.84)
0.47[f] (0.14–0.90)	1.97[f] (1.21–2.95)	0.95 (0.60–1.36)
NA[d]	NA[d]	0.09[g,h] (0.03–0.15)
0.02 (−0.01–0.11)	−0.06 (−0.10–0.07)	0.00 (−0.06–0.07)
0.20[h] (−0.04–0.7)	—	0.20[i] (−0.04–0.7)
NA[d]	NA[d]	0.24 (0.07–0.44)
—	0.20 (−0.62–1.03)	0.20 (−0.62–1.03)
—	0.38 (<0–0.6)	0.38 (<0–0.6)

in risk estimates reported in these studies. These include differences in baseline lung cancer rates, especially the lower rates among Japanese (*22*); differences in the magnitude of the doses; fractionation of exposure in all except the A-bomb survivor study; differences in dose rate; any residual role of other exposures such as smoking or alkylating agent chemotherapy; and statistical variation, which in itself could explain much of the variation. We also note that variation in doses to different parts of the lung is likely to be somewhat greater in our study than in the others shown in Table 5, particularly for the A-bomb survivors (*5, 6*) and Mayak workers (*18*) who were exposed to whole-body radiation. Our study is unique in its estimation of radiation dose to the precise location of the tumor in individual patients and in its inclusion of data on tobacco use. Estimates from our study are smaller than those based on A-bomb survivors but are in reasonable agreement with those derived from investigations of ankylosing spondylitis patients (*16*) and women treated for breast cancer (*20*), where radiation doses were also high, fractionated and heterogeneous. Since increased risks of lung cancer have been reported in immunocompromised hosts (reviewed in ref. *1*), immunodeficiency associated with Hodgkin's disease and its treatment (*23*) might serve to dampen the ERR/Gy.

Our study offers an unusual opportunity to investigate the interaction between radiation and exposure to alkylating agents. Similar to our previous analyses (*1*) based on qualitative measures of exposure, the effects of radiation and alkylating agents on lung cancer were almost exactly additive, and a multiplicative interaction could be rejected. The molecular mechanisms of radiation carcinogenesis of the lung are unclear. However, in a study of 19 secondary lung cancers from the present series, Behrens *et al.* (*24*) reported a significantly increased, 2.4-fold frequency of microsatellite alterations compared with sporadic lung cancers, consistent with widespread genomic instability resulting from radiation exposure and lung immunosuppression.

The means by which alkylating agents contribute to molecular events leading to lung cancer are not known, but may involve direct reaction with DNA bases to produce single-strand and double-strand breaks (*25*). Methylating agents, such as procarbazine, can form the same type of DNA adduct [O^6-methylguanine (*26*)] that is produced by the tobacco metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a pulmonary carcinogen in preclinical studies (*27*). An increased risk of lung cancer has been associated with deficient repair of O^6-methylguanine adducts (*28*) including that associated with polymorphisms in the cellular enzyme O^6-methylguanine methyl transferase (*29*).

In contrast to the additive effect of radiation and alkylating agents, a similar relationship between radiation and smoking risks could be rejected. Based on analyses of data on lung cancer mortality in A-bomb survivors conducted more than a decade ago, it was not possible to distinguish between additive and multiplicative models for the interaction of smoking and radiation (*30–32*). However, among underground miners exposed to α-particle emitters from radon, an additive interaction of smoking and radiation could be rejected, with the interaction estimated to be sub-multiplicative, although a multiplicative association could not be rejected (*33*). When Thomas *et al.* (*34*) analyzed data on the Colorado Plateau miners, the interaction appeared additive when exposure to radon was followed by smoking, but multiplicative when smoking was followed by radon. In our study, all subjects who smoked did so before their diagnosis of Hodgkin's disease; some, but not all, continued to smoke after their diagnosis.

In a study of Hodgkin's disease survivors, van Leeuwen *et al.* (*2*) found evidence of a super-multiplicative interaction of smoking and radiation. A radiation dose response was demonstrated only for patients who had smoked one or more pack-years after Hodgkin's disease diagnosis, and the dose response for these patients differed significantly from that observed for patients who did not smoke after Hodgkin's disease diagnosis. Most patients in this latter category would have been either former smokers or never-smokers in our study. Also, subjects in our unknown category (who had no information on smoking in their medical records) are probably more likely to be never-smokers or former smokers than current smokers. When these three categories (never, former and unknown) were combined, we found a statistically significant association with radiation dose. The higher ERR/Gy among current smokers with more than 32 pack-years in our study may suggest a super-multiplicative relationship; however, this was not confirmed in analyses based only on data on smoking collected near the time of Hodgkin's disease diagnosis.

In our study, we could not reliably evaluate differences in effects of smoking before and after Hodgkin's disease diagnosis. Of the 455 subjects who were not included in the study by van Leeuwen *et al.* (*2*) and whose lung cancer diagnosis was at least 5 years after their Hodgkin's disease diagnosis, 95 (21%) had no data on smoking, and 142 (31%) had data on smoking collected only in the first year after Hodgkin's disease. However, analyses based on data collected within a year of Hodgkin's disease diagnosis showed clear evidence of an effect of smoking, in contrast

to the finding by van Leeuwen *et al.* (*2*) of no relationship between lung cancer risk and smoking prior to Hodgkin's disease diagnosis. It is likely that some of the negative findings in the study of van Leeuwen *et al.* (*2*) were due to the small study size (30 cases) and the resulting low statistical power.

Although the difference in ERR/Gy for males and females does not approach statistical significance, it is in the opposite direction from most other studies. Lung cancer ERR/Gy for females were larger than those for males in A-bomb survivors (Table 5) and in ankylosing spondylitis patients, although in the latter group, the difference was not statistically significant and sex-specific ERR/Gy were not presented. Swerdlow *et al.* (*35*) also reported that the relative risk for lung cancer (compared with national rates) was significantly larger among females, although this would have reflected the effects of both radiotherapy and chemotherapy. These gender differences may largely reflect gender differences in baseline lung cancer rates; in most western countries and in Japan, rates for males are at least a factor of two higher than rates for females (*22*). Unlike the studies noted above, our analyses were adjusted for smoking. Further, with a multiplicative interaction of smoking and radiation exposure, one would not expect the ERR to depend on smoking habits or gender, since smoking habits are probably the primary contributor to gender differences in baseline risks. However, the larger ERRs observed for females in other investigations suggest that the interaction of radiation and smoking may be less than multiplicative in these studies.

Another issue of interest for radiation risk assessment is the pattern of excess risks over time. Data on ankylosing spondylitis patients have demonstrated a clear drop in excess lung cancer risk 25 years from exposure (*16*), but there is little indication of such a decline among A-bomb survivors (*5*). Inskip *et al.* (*20*) observed the largest relative risks for lung cancer among breast cancer patients after for 20 or more years. Our study showed that risk persists for at least 20 years after exposure with little evidence of a decline. Although the ERR/Gy for the 20+ year time-since-exposure category is lower than for earlier periods (Table 4D), the difference does not approach statistical significance ($P > 0.5$). Follow-up in our study was insufficient to evaluate risks after 25 years since only 4 cases occurred in this period.

Among cancer sites evaluated in A-bomb survivors, lung cancer is exceptional in the absence of a decline in the ERR with increasing age at exposure or with increasing attained age (*4–6*). A decline with attained age has been observed, however, in studies of lung cancer in underground miners exposed to α-particle emitters (*33*). In our study, age at exposure and attained age are correlated so that patterns for these two variables are similar (Table 4F and 4G). We found little evidence of decline with either variable, although the ERR/Gy in the youngest age groups (Table 4F and 4G) were nonsignificantly larger than the average values. Swerdlow *et al.* (*35*) reported a decline in lung cancer risk with increasing age at radiation exposure, based mainly on large relative risks among those treated before age 25. In our study, only one case was diagnosed with Hodgkin's disease before age 20, and an additional seven cases were diagnosed between ages 20 and 25; all eight patients were treated with radiation and all but one had doses that exceeded 30 Gy, making it impossible to reliably evaluate radiation risks in this group. An increase in risk with increasing age at exposure or attained age was suggested for patients in the three highest age quartiles; this might result from chance variation, but it could also be due a complex interaction of the effects of smoking, age and radiation exposure.

There was no evidence of variation in the ERR/Gy by the histopathological type of lung cancer, similar to the findings for A-bomb survivors (*5*) and breast cancer patients (*20*). However, adenocarcinoma was the most common type of lung cancer in A-bomb survivors (about 44% of lung cancer cases in both exposed and unexposed), whereas the most common type in our study was squamous cell carcinoma (45% of cases). Variation in radiation-associated risk by type of lung cancer was not evaluated in other studies shown in Table 5 (*16–19, 21*).

The estimates of radiation dose to the precise location where the lung tumor was diagnosed were higher than the more easily estimated average doses to the lobe of the lung where the tumor was located. In addition, higher statistical power was achieved in analyses based on doses to the precise tumor location compared with analyses based on average doses. Although in our study the use of average lung doses yielded adequate statistical power to detect a dose response, this might not be the case in a smaller study with fewer cases. A major determinant in doses to the precise tumor location is the distance from the tumor site to the edge of the nearest radiation field or to the edge of a block. Thus any inaccuracies in tumor location can lead to inaccuracies in estimated doses. For tumors that are located near an edge, a small change in distance can lead to a 10-fold change in dose. Nevertheless, estimates of the ERR/Gy based on patients whose tumors were not located near an edge were similar to those based on all subjects.

Our study is subject to several limitations. Some patients did not have sufficient information for radiation dose estimation and had to be excluded. Dose estimates for some of the remaining patients were subject to uncertainties in the precise location of the tumor relative to radiation fields and blocking. Many subjects were treated with chemotherapy as well as radiotherapy. Although we are reasonably confident that adjustment for the effects of chemotherapy was adequate, the lack of an untreated control group is nevertheless a limitation. Data on smoking were limited to information abstracted from medical sources and were not systematically recorded in formats that would be optimal for epidemiological studies. Further, records with smoking information often failed to cover the full period from Hodg-

kin's disease diagnosis to lung cancer diagnosis. Data were particularly limited for estimation of the duration of smoking, so that our *pack-year* variable was based primarily on age of the subject at lung cancer diagnosis. Nevertheless, these data were adequate to demonstrate a strong effect of smoking, and results based only on data collected near the time of Hodgkin's disease diagnosis (with little chance of differential ascertainment for cases and controls) did not differ greatly from results based on data collected up to 1 year prior to lung cancer diagnosis. Further, our information on smoking is superior to that available in most other studies, where data on smoking were either lacking entirely (*5, 6, 16–21*) or were limited to never/ever indicators of smoking (*8, 9*). Although quantitative estimates from our study should be interpreted cautiously, it seems unlikely that our findings on interactions of smoking and radiation are seriously distorted.

In spite of these limitations, our study, with its large size, quantitative data on radiation dose, chemotherapy and smoking, and the large relative risks associated with all three variables, provided an unusual opportunity to investigate the radiation dose–response relationship and potential modifying factors. Our emphasis on quantitative measures (radiation dose, number of cycles, pack-years) has allowed a more rigorous evaluation of issues of interest for radiation risk assessment than our previous report (*1*). We know of no other study that has addressed the interaction of radiation dose and exposure to alkylating agents in determining lung cancer risks, and this is the only study in which it has been possible to distinguish between additive and multiplicative models for the interaction of smoking and exposure to low-LET radiation. It must be kept in mind, however, that considerable uncertainty exists in applying our findings based on immunodeficient Hodgkin's disease patients given very high doses of radiation to general populations receiving much lower doses.

APPENDIX

Radiation Dosimetry

For radiation dosimetry, the aim was to estimate the dose to the site of the secondary lung tumor for each case and to the comparable anatomical point in controls matched to that case. For each patient in the study who received radiotherapy, we requested a copy of the full radiotherapy record, which included simulator films of chest fields, treatment plans, daily logs, field diagrams, and machine parameters. The record was abstracted for details of treatment and evaluated for completeness. To locate the subsequent lung tumor for cases, we requested copies of computed tomography (CT) and radiographic films and/or reports of these examinations. The most useful information for locating lung tumors was derived from CTs and radiographs, supplemented by information from pathology reports, bronchoscopy records, clinical notes and/or diagrams, and autopsy findings.

Appendix Table 1 summarizes information on the status of radiation dose estimates. Of 616 patients who received radiotherapy, 59 had doses that could not be estimated because either available radiotherapy records contained insufficient detail or the precise location of the lung tumor could not be determined. Most of these 59 patients were excluded from our analyses. However, as indicated in the Statistical Methods section, most analyses are based on the 5-year lagged dose, where dose received in the 5 years preceding the date of lung cancer diagnosis (or comparable date in the controls) is excluded. Thus, except for analyses addressing time-since-exposure effects, subjects who received their entire radiation dose in this period could be included regardless of whether data were adequate for dose estimation. As shown in Appendix Table 1, a total of 48 subjects (22 cases, 26 controls) were excluded because their 5-year lagged doses could not be estimated. An additional 23 controls who were matched to cases whose doses could not be estimated and one case matched to two controls whose doses could not be estimated were also excluded because they were uninformative in matched analyses. Thus analyses based on 5-year lagged doses include a total of 682 patients (227 cases and 455 controls). Numerical results in the material that follows pertain to the 146 cases and 271 controls with positive 5-year lagged

APPENDIX TABLE 1
Numbers of Lung Cancer Cases and Matched Controls by whether or not Radiation Dose Could be Estimated

Category	Cases	Controls	Totals
Dose could be estimated	183 (182[a])	374 (361[b])	557 (543)
5-year lagged dose positive	147 (146[a])	284 (271[b])	431 (417)
5-year lagged dose zero[c,d]	36 (36)	90 (90)	126 (126)
Dose could not be estimated[e]	24 (2)	35 (7)	59 (9)
5-year lagged dose would have been positive	22 (0)	26 (0)	48 (0)
5-year lagged dose would have been zero[c]	2 (2)	9 (7[b])	11 (9)
No radiation therapy[f]	43 (43)	95 (87[b])	138 (130)
Total	250 (227)	504 (455)	754 (682)

Note. Numbers in parentheses indicate subjects who were included in analyses based on 5-year lagged dose.

[a] One case was excluded because both of the matched controls had doses that could not be estimated.

[b] Some controls were excluded because their matched cases had doses that could not be estimated.

[c] All dose was received in the 5 years prior to lung cancer diagnosis (or comparable date in controls).

[d] For 33 cases and 77 controls, the time between Hodgkin's disease and lung cancer diagnosis was less than 5 years; for 3 cases and 13 controls this interval was 5 or more years.

[e] For 21 subjects (11 cases and 10 controls), radiotherapy records were inadequate for reliable dose estimation. For 44 subjects (16 cases and 28 controls), the tumor location for the case was insufficiently known for reliable radiation dosimetry. Six subjects (3 cases and 3 controls) had both deficiencies, and thus are included in both the previous counts.

[f] Among the 43 cases and 87 controls included in analyses, the time between Hodgkin's disease and lung cancer diagnosis was less than 5 years for 19 cases and 24 controls; for 24 cases and 63 controls, this interval was 5 or more years.

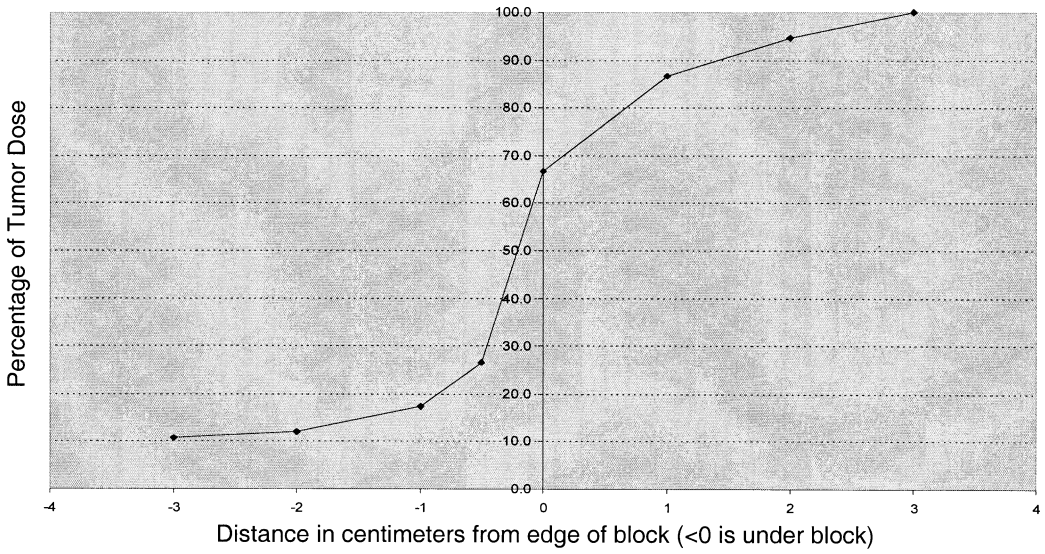

FIG. A1. Absorbed dose across a typical blocked field, relative to the tumor dose.

doses whose data were included in analyses presented in the body of the paper.

Of importance for this study is the fact that 83% of the Hodgkin's disease patients had all or part of their treatments to the chest; 89% of the chest treatment included large fields with lung blocks or a series of small fields treating lymph node regions above the diaphragm. Photon beam energies used were megavoltage (4–10 MV) in 51% of patients; cobalt-60, 42%; betatron (20–33 MV), 3%; and orthovoltage (170 to 250 kVp), 4%. Electron beams were used for a few patients (1%) in addition to photons. In general, the treatment modalities were typical of the 1970s and 1980s.

The radiation oncologist (MG), together with other collaborators, located the tumor site in each patient by reviewing all available documentation. MG also estimated the size of the tumor in the AP view; all radiation doses were estimated to the center of the tumor. For blocked chest fields, simulator films were the most useful source of information. The major determinant of dose to the lung tumor site was the distance from that site to the nearest field or block edge

For each patient in a case/control set, we estimated the absorbed radiation dose to the specific site of the lung cancer in the case. Most chest treatments used anterior and posterior fields, resulting in a reasonably uniform dose across lung depth. Therefore, for all patients the dose was calculated to a midpoint in the anterior–posterior direction. Treatment beams were of two types: (1) open beams defined by collimators only and (2) beams with additional blocking to form irregular shapes, i.e. mantle fields. Treatment-planning systems (Nucletron RTS, Version 6.36, and ADAC Pinnacle-3, Version 4.0), which take into account attenuation of radiation by blocks, were used to approximate the dose gradient across a blocked field; Fig. A1 shows the dose gradient as a percentage of tumor dose. The dose outside the beams was calculated using mathematical modeling of a three-dimensional phantom, using data measured in water phantoms (*36*). All calculations were based on the tumor dose and radiation energy reported in the patient's record. For each patient the doses from all radiotherapy fields were summed.

Dosimetry data used in this study are typical for the period during which the study subjects were treated and are not suitable for current treatment planning for individual patients. Dose estimates are subject to uncertainties resulting from limitations in retrospective evaluation of treatments and tumor locations. However, doses were calculated consistently for all subjects, both cases and controls, and allowed informative dose–response analyses of secondary lung tumors.

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